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EXAMINER	
GOON, SCARLETT Y	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/586,345	REINMULLER ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 22-26* is/are pending in the application.

4a) Of the above claim(s) *7,8,10,22 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9,11-13,23,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to Applicants' Amendment and Remarks filed on 23 March 2010 in which claims 14-21 were cancelled, claim 5 is amended to change the scope and breadth of the claims, and new claims 25 and 26 are added.

The Declaration of Dr. Johannes Reinmüller (inventor), submitted by Applicants on 28 April 2010 under 37 CFR § 1.132, are acknowledged and will be further discussed below.

Claims 1-13 and 22-26 are pending in the instant application.

Claims 7, 8 and 10 were previously withdrawn from further consideration in the Office Action dated 24 October 2008 pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 22 and 24 were previously withdrawn from further consideration in the Office Action dated 14 April 2009 pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 1-6, 9, 11-13, 23, 25 and 26 will be examined on its merits herein.

Priority

This application is a National Stage entry of PCT/EP2005/000215 filed on 12 January 2005 and claims priority to Germany foreign application 10 2004 002 001.9 filed on 14 January 2004. A certified copy of the foreign priority document in German has been received. No English translation has been received.

Rejections Withdrawn

Applicants' arguments, filed 23 March 2010, with respect to the rejection of claim 5 under 35 USC § 103(a), as being unpatentable over PG Pub No. US 2004/0136925 A1 to Petrigni *et al.*, in view of U.S. Patent No. 4,716,224 to Sakurai *et al.*, as applied to claims 1-4, 6, 9 and 11-13, further in view of chapter publication by Wilkinson, have been fully considered and are persuasive because the combined teachings of the prior art do not provide any evidence to support that uncrosslinked hyaluronic acid actually takes effect faster in the organism than crosslinked hyaluronic acid. This rejection has been **withdrawn**.

Applicants' arguments, filed 23 March 2010, with respect to the rejection of claims 5 and 6 under 35 USC § 103(a), as being unpatentable over U.S. Patent No. 5,914,322 to Falk *et al.*, in view of U.S. Patent No. 4,716,224 to Sakurai *et al.*, in view of U.S. Patent No. 6,455,066 B1 to Fischer *et al.*, as applied to claims 1-4, 9, 11-13 and 23, further in view of chapter publication by Wilkinson, have been fully considered and are persuasive because the combined teachings of the prior art do not provide any evidence to support that uncrosslinked hyaluronic acid actually takes effect faster in the organism than crosslinked hyaluronic acid. This rejection has been **withdrawn**.

These rejections have been **withdrawn**.

The following are new ground(s) of rejections.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 9, 11 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by DE 10209966 A1 to Reinmüller (IDS dated 25 February 2009; EPO machine translation of foreign document included herewith).

Reinmüller discloses the use of crosslinked or uncrosslinked hyaluronic acid in a pharmaceutical composition for the treatment of viral infections, particularly herpes viruses (p. 1, paragraph 1). The preferred molecular weight of hyaluronic acid is between 10^4 to 10^6 Da, preferably between 10^5 to 10^6 Da (p. 2, paragraph 2). With such a molecular weight, the degree of crosslinking can remain small (p. 2, paragraph 2). The pharmaceutical composition can comprise between 0.01 to 20% of hyaluronic acid (p. 2, paragraph 5). The composition is suitable for both systemic and local applications. The composition in the form of a gel can be administered by intradermal or subdermal injection to the affected area, for treatment of infections from neurotropic viruses, including herpes viruses (p. 3, paragraphs 5 and 6).

Thus, the use of crosslinked or uncrosslinked hyaluronic acid in a pharmaceutical composition for the treatment of herpes viruses, disclosed by Reinmüller, anticipates claims 1-3, 9, 11 and 26.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Section [0001]

Claims 5, 6 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over DE 10209966 A1 to Reinmüller (IDS dated 25 February 2009; EPO machine translation of foreign document included herewith), as applied to claims 1-3, 9, 11 and 26.

The teachings of Reinmüller were as disclosed above in the claim rejections under 35 USC § 102.

The teachings of Reinmüller differ from that of the instantly claimed invention in that Reinmüller does not expressly teach that the composition comprises hyaluronic acid in both crosslinked and uncrosslinked forms.

However, Reinmüller expressly teaches that both crosslinked hyaluronic acid and uncrosslinked hyaluronic acid are useful for the treatment of infections from neurotropic viruses, such as herpes viruses. Thus, it would have been *prima facie* obvious for one of ordinary skill in the art to make a composition comprising both crosslinked and uncrosslinked hyaluronic acid, with the expectation that the combination would also be useful for the treatment of herpes viruses. See below for recitation of section from MPEP § 2144.06 regarding combining equivalents known for the same purpose.

The following is a quotation of MPEP § 2144.06:

> I. >< COMBINING EQUIVALENTS KNOWN FOR THE SAME PURPOSE
> "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be *prima facie* obvious.). *See also In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held *prima facie* obvious).

Thus, the instantly claimed invention is prima facie obvious over the teachings of Reinmüller.

Section [0002]

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over DE 10209966 A1 to Reinmüller (IDS dated 25 February 2009; machine translation), as applied to claims 1-3, 9, 11 and 26, further in view of U.S. Patent No. 4,713,448 to Balazs (hereinafter referred to as the '448 patent; PTO-892, Ref. A).

The teachings of Reinmüller were as disclosed above in the claim rejections under 35 USC § 102.

The teachings of Reinmüller differ from that of the instantly claimed invention in that Reinmüller does not expressly teach a specific degree of crosslinking for the hyaluronic acid.

However, Reinmüller expressly teaches that the degree of crosslinking can remain small when the molecular weight of hyaluronic acid is in the range from 10^5 and 10^6 (p. 2, paragraph 2), and that hyaluronic acid in a crosslinked state can be prepared using methods such as that described in U.S. Patent No. 4,713,448 to Balazs *et al.*

The Balazs '448 patent teaches the preparation of hylan, a chemically modified hyaluronic acid preparation characterized by the presence of small amounts (0.005-0.05% by weight) of aldehyde crosslinking groups covalently bonded to the hyaluronic acid molecular chains.

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Reinmüller, concerning the use of crosslinked and/or uncrosslinked hyaluronic acid in the treatment of herpes virus infection, with the teachings of the Balazs '448 patent, regarding methods for the preparation of hylan. Since Reinmüller teaches that the degree of crosslinking can remain small when the molecular weight of hyaluronic acid is in the range from 10^5 and 10^6, and Reinmüller further teach that methods for the preparation of crosslinked hyaluronic acid can be found, *inter alia*, in the Balazs '448 patent, it would have been *prima facie* obvious for one of ordinary skill in the art to look to the Balazs '448 patent for guidance on the degree of crosslinking of hyaluronic acid.

It is noted that the Balazs '448 patent does not expressly teach a degree of crosslinking in the range of 0.1% to 10%, as recited in the instant claims. However, the Balazs '448 patent expressly teaches a degree of crosslinking in the range from 0.005% to 0.05%. The Courts have found that "a *prima facie* case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties." See MPEP § 2144.05 [R-5]. In *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), the Court held as proper a rejection of a claim directed to an alloy of "having 0.8% nickel, 0.3% molybdenum, up to 0.1% iron, balance titanium" as obvious over a reference disclosing alloys of 0.75% nickel, 0.25% molybdenum, balance titanium and 0.94% nickel, 0.31% molybdenum, balance titanium. In the instant

case, the instantly claimed degree of crosslinking of 0.1% is considered to be obvious over the crosslinking degree of 0.05% taught in the Balazs '448 patent.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0003]

Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over DE 10209966 A1 to Reinmüller (IDS dated 25 February 2009; machine translation), as applied to claims 1-3, 9, 11 and 26, further in view of journal publication by Stanberry (PTO-892, Ref. U).

The teachings of Reinmüller were as disclosed above in the claim rejections under 35 USC § 102.

The teachings of Reinmüller differ from that of the instantly claimed invention in that Reinmüller does not expressly teach that the patient population treated using the hyaluronic acid composition include humans and veterinary animals, as instantly claimed.

Stanberry discloses a study on the evaluation of herpes simplex virus vaccines in a guinea pig model. The guinea pig has become a very useful model for exploring the immunobiology of genital herpes (p. S920, column 2, last sentence). Genital herpes in guinea pigs shares many similarities with genital herpes in humans, including a natural route of inoculation and self-limiting quantifiable genital skin disease that is associated with neurological and urologic complications (p. S920, column 1, second paragraph).

The guinea pig has been useful for the study of the effect of immunogen composition, dose, route of administration, and adjuvant formation on vaccine efficacy (p. S921, column 1, paragraph 2).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Reinmüller, concerning the use of crosslinked and/or uncrosslinked hyaluronic acid in the treatment of herpes virus infection, with the teachings of Stanberry, regarding the evaluation of herpes simplex virus vaccines in a guinea pig model. Since Stanberry teaches the availability of a guinea pig model in evaluating herpes simplex virus vaccines due to the similarity of the virus in both guinea pigs and humans, one of ordinary skill in the art would have been motivated to evaluate the hyaluronic acid composition in the guinea pig model prior to use on humans to optimize dosage and efficacy. Furthermore, one of ordinary skill in the art would have had a reasonable expectation of success in using the composition comprising hyaluronic acid, either crosslinked or uncrosslinked, for the treatment of herpes virus in guinea pigs or humans, because Reinmüller teaches that the hyaluronic acid composition is useful for the treatment of infections from neurotropic viruses, including herpes viruses.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

The following rejections of record in the previous Office Action are maintained.

Section [0004]

Claims 1-4, 9 and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over PG Pub No. US 2004/0136925 A1 to Petrigni *et al.* (of record), in view of U.S. Patent No. 4,716,224 to Sakurai *et al.* (hereinafter referred to as the '224 patent, of record).

Petrigni *et al.* teach pharmaceutical preparations containing a suitable mixture, in colloidal form, of biopolymerized hyaluronic acids as the active ingredient, having defined and different molecular weights and being dispersed in suitable diluents, and their use in the treatment of pathological cutaneous diseases (paragraph 0001 and 0010). The pharmaceutical preparation in colloidal liquid form is preferably administered by topical route, but may also be conveniently administered through a general route, such as subcutaneous intramuscular intradermal infection, or in a solid form by oral route or as a transdermal plaster by transcutaneous route (paragraph 0012). The hyaluronic acids of the mixture have molecular weights ranging from 200 kDa to 4,000 kDa. Petrigni *et al.* further exemplified the treatment of *acne vulgaris* (paragraphs 0023-0027), contact eczema (paragraphs 0028-0032) and atopical eczema (paragraphs 0033-0042) using the disclosed pharmaceutical preparation.

Although Petrigni *et al.* specifically teach that the pharmaceutical preparation comprises biopolymerized hyaluronic acids, it appears from the disclosed preparation procedure (Example 1, paragraph 0015-0020) that the hyaluronic acids were not crosslinked and thus "biopolymerized hyaluronic acids" merely refers to the typical

polymeric form of hyaluronic acid. Therefore, the teachings of Petrigni *et al.* differ from that of the instantly claimed invention in that the hyaluronic acid is not present in crosslinked form.

The Sakurai '224 patent teaches that the hyaluronic acid typically administered to a subject is isolated and purified from a source and lacks the stringiness and viscoelasticity of hyaluronic acid typically found in the living body (column 1, lines 35-40). Moreover, hyaluronic acid is known to undergo enzymatic decomposition or non-enzymatic oxidation-reduction decomposition after being administered to a living body, especially at diseased sites (column 1, lines 41-44). Crosslinked hyaluronic acid, on the other hand, shows resistance to enzymatic decomposition or non-enzymatic oxidation-reduction decomposition (column 1, lines 54-59). Thus, crosslinked hyaluronic acid has a wide variety of medical and cosmetic uses (column 1, lines 61-63). The crosslinking index (percent of crosslinking) of the resultant crosslinked hyaluronic acid or salt thereof from a reaction, may be controlled by varying the molar ratio of the hyaluronic acid, or salt thereof, to the polyfunctional epoxy compound used for crosslinking (column 3, lines 3-6). The cosmetic containing crosslinked hyaluronic acid may be in the form of a cream, lotion, or hair cosmetic (column 4, lines 30-33). Example 8 illustrates the use of crosslinked hyaluronic acid on rabbits (column 10, lines 14-68).

The Sakurai '224 patent discloses crosslinked hyaluronic acid with varying degrees of crosslinking, as indicated by their crosslinking index. For example, crosslinked hyaluronic acids with a crosslinking index per 1000 repeating disaccharides in hyaluronic acid of 8.5, 7.5, 13 and 40 and disclosed in Examples 1-4, respectively.

Moreover, the Sakurai '224 patent teaches that the degree of crosslinking may be controlled by varying the molar ratio of the hyaluronic acid, or salt thereof, to the polyfunctional epoxy compound used for crosslinking (column 3, lines 3-6). Thus, it is considered that one of ordinary skill in the art would have the capabilities of adjusting their reaction to obtain a crosslinked hyaluronic acid with the desired percent of crosslinking.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Petrigni *et al.*, concerning a pharmaceutical composition comprising hyaluronic acids and its use in the treatment of pathological cutaneous diseases, such as eczema or *acne vulgaris*, with the teachings of the Sakurai '224 patent, regarding the enzymatic decomposition and non-enzymatic oxidation-reduction of hyaluronic acid after being administered to a living body and how crosslinked hyaluronic acid is resistant to such decomposition. One would have been motivated to combine the teachings and crosslink the hyaluronic acids in the composition disclosed in Petrigni *et al.*, in order to receive the expected benefit, as suggested in the Sakurai '224 patent, that crosslinked hyaluronic acid shows resistance to enzymatic decomposition or non-enzymatic oxidation-reduction decomposition (column 1, lines 54-59). Thus, one of ordinary skill in the art would know that the compound's half-life would be increased as it is no longer subjected to enzymatic and non-enzymatic oxidation-reduction decomposition, which one of ordinary skill in the art would generally view as a positive pharmacokinetic property of drugs.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicants' arguments, filed 23 March 2010, and the Declaration of Mr. Johannes Reinmüller, submitted by Applicants on 28 April 2010 under 37 CFR § 1.132, with respect to the rejection of claims 1-4, 9 and 11-13 made under 35 USC § 103(a) as being unpatentable over PG Pub No. US 2004/0136925 A1 to Petrigni *et al.*, in view of U.S. Patent No. 4,716,224 to Sakurai *et al.*, have been fully considered but they are not persuasive.

Applicants argue that one of ordinary skill in the art would not have considered intradermally administering crosslinked hyaluronic acid due to the latter having completely different properties as compared to uncrosslinked hyaluronic acid. Specifically, Applicants argue that crosslinked hyaluronic acid, due to crosslinking and its high molecular weight, has a high viscosity and thus, is a jelly-like compound which behaves like a solid, and therefore does not laminarly distribute within the tissue following intradermal administration. Applicants further submitted a Declaration by Mr. Reinmüller attesting to the effect. Applicants' arguments and the Declaration of Mr. Reinmüller have been carefully reviewed but are not considered persuasive. Prior to the time of the instant invention, DE 10209966 in 2003 discloses intradermal administration of crosslinked hyaluronic acid for the treatment of herpes virus. Thus, contrary to Applicants' arguments, based on what was known in the art prior to the time

of Applicants' invention, one of ordinary skill in the art would consider combining the teachings of Petrigni *et al.* and the Sakurai '224 patent for treatment of inflammatory skin diseases via intradermal injection as DE 10209966 has already disclosed that such a means of administration is effective.

Therefore, the Declaration of Mr. Johannes Reinmüller is ineffective to rebut the *prima facie* case herein.

The rejection is still deemed proper and therefore maintained.

Section [0005]

Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over PG Pub No. US 2004/0136925 A1 to Petrigni *et al.* (of record), in view of U.S. Patent No. 4,716,224 to Sakurai *et al.* (hereinafter referred to as the '224 patent, of record), as applied to claims 1-4, 6, 9 and 11-13, further in view of journal publication by Sterling *et al.* (of record).

The teachings of Petrigni *et al.* and the Sakurai '224 patent were as disclosed in section [0001] of the claim rejections under 35 USC § 103.

The combined teachings of Petrigni *et al.* and the Sakurai '224 patent differ from that of the instant invention in that they do not teach a pathological cutaneous disease which is a viral skin disease leading to wart formation.

Sterling *et al.* teach that cutaneous warts are caused by the infection of the epidermis with human papillomarvirus (HPV) (p. 4, column 1, subheading "Definition," first paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Petrigni *et al.*, concerning a pharmaceutical composition comprising hyaluronic acids and its use in the treatment of pathological cutaneous diseases, such as eczema or *acne vulgaris*, with the teachings of the Sakurai '224 patent, regarding the enzymatic decomposition and non-enzymatic oxidation-reduction of hyaluronic acid after being administered to a living body and how crosslinked hyaluronic acid is resistant to such decomposition, with the teachings of Sterling *et al.*, regarding cutaneous warts being caused by HPV. Since Sterling *et al.* teach that warts are a pathological cutaneous disease and Petrigni *et al.* teach that the disclosed composition comprising hyaluronic acid can be administered in the treatment of pathological cutaneous diseases, one would have been motivated to combined the teachings and administer the composition comprising hyaluronic acid to a patient with warts, with the expectation that since warts are a pathological cutaneous disease, the composition comprising hyaluronic acid would also be successful in the treatment of warts. One would have been further motivated to combine the teachings and crosslink the hyaluronic acids in the composition disclosed in Petrigni *et al.*, in order to receive the expected benefit, as suggested in the Sakurai '224 patent, that crosslinked hyaluronic acid shows resistance to enzymatic decomposition or non-enzymatic oxidation-reduction decomposition (column 1, lines 54-59), as disclosed above.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicants' arguments, filed 23 March 2010, with respect to the rejection of claim 23 made under 35 USC § 103(a) as being unpatentable over PG Pub No. US 2004/0136925 A1 to Petrigni *et al.*, in view of U.S. Patent No. 4,716,224 to Sakurai *et al.*, as applied to claims 1-4, 9 and 11-13, have been fully considered but they are not persuasive. The Declaration of Mr. Johannes Reinmüller, submitted by Applicants on 28 April 2010 under 37 CFR § 1.132, was previously addressed with respect to the parent claims.

Applicants argue that Petrigni *et al.* disclose a composition for treating pathological skin disease by means of hyaluronic acid, but is silent regarding the treatment of skin diseases caused by viral infections. Thus, Applicants argue that a skilled person would not expect the composition of Petrigni *et al.* to be also suitable for treating viral disease, which is different from inflammation caused by allergens, such as that with dermatitis and acne. This argument is not persuasive because Petrigni *et al.* expressly state that the disease is also useful for the treatment of ulcerous eruptions and Herpes simplex (paragraph 0010), a viral disease. Thus, contrary to Applicants' argument, as Petrigni *et al.* expressly teach that their composition is useful in the treatment of herpes simplex, a viral disease, one of ordinary skill in the art would have a reasonable expectation that the disclosed composition would also be useful in treating cutaneous warts, a viral disease caused by the human papilloma virus.

The rejection is still deemed proper and therefore maintained.

Section [0006]

Claims 1-4, 9, 11-13 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,914,322 to Falk *et al.* (hereinafter referred to as the '322 patent, of record), in view of U.S. Patent No. 4,716,224 to Sakurai *et al.* (hereinafter referred to as the '224 patent, of record), in view of U.S. Patent No. 6,455,066 B1 to Fischer *et al.* (hereinafter referred to as the '066 patent, of record).

The Falk '322 patent discloses that a therapeutically effective amount of hyaluronic acid in a composition is useful in the treatment of skin diseases and conditions by topically administering said composition to a subject. The topical composition may be used to treat diseases and conditions of the skin such as genital warts cervical cancer, human papilloma virus (HPV), and psoriasis, among others (column 7, lines 10-22; column 12, lines 28-39). The composition may be in any suitable form, such as a lotion or a cream (column 8, lines 61-62). As shown in Formulation (A), the weight of sodium hyaluronate is 661,600 (661 kDa) (column 13, lines 10-23). Examples 1-7 illustrate the use of the composition on human patients with lesions (Examples 1-3) or psoriasis (Example 7) (columns 25 and 26).

The Falk '322 patent does not explicitly teach that hyaluronic acid is in the crosslinked form or that it is administered intradermally.

The Sakurai '224 patent teaches that the hyaluronic acid typically administered to a subject is isolated and purified from a source and lacks the stringiness and viscoelasticity of hyaluronic acid typically found in the living body (column 1, lines 35-40). Moreover, hyaluronic acid is known to undergo enzymatic decomposition or non-

enzymatic oxidation-reduction decomposition after being administered to a living body, especially at diseased sites (column 1, lines 41-44). Crosslinked hyaluronic acid, on the other hand, shows resistance to enzymatic decomposition or non-enzymatic oxidation-reduction decomposition (column 1, lines 54-59). Thus, crosslinked hyaluronic acid has a wide variety of medical and cosmetic uses (column 1, lines 61-63). The crosslinking index (percent of crosslinking) of the resultant crosslinked hyaluronic acid or salt thereof from a reaction, may be controlled by varying the molar ratio of the hyaluronic acid, or salt thereof, to the polyfunctional epoxy compound used for crosslinking (column 3, lines 3-6). The crosslinked hyaluronic acid may be used in skin cosmetics (column 4, lines 4-6), for application on, for example, shaving, cracking, and chappy skin (column 4, lines 28-30). The cosmetic containing crosslinked hyaluronic acid may be in the form of a cream, lotion, or hair cosmetic (column 4, lines 30-33). Example 8 illustrates the use of crosslinked hyaluronic acid on rabbits (column 10, lines 14-68).

The Sakurai '224 patent discloses crosslinked hyaluronic acid with varying degrees of crosslinking, as indicated by their crosslinking index. For example, crosslinked hyaluronic acids with a crosslinking index per 1000 repeating disaccharides in hyaluronic acid of 8.5, 7.5, 13 and 40 and disclosed in Examples 1-4, respectively. Moreover, the Sakurai '224 patent teaches that the degree of crosslinking may be controlled by varying the molar ratio of the hyaluronic acid, or salt thereof, to the polyfunctional epoxy compound used for crosslinking (column 3, lines 3-6). Thus, it is considered that one of ordinary skill in the art would have the capabilities of adjusting

their reaction to obtain a crosslinked hyaluronic acid with the desired percent of crosslinking.

The Fischer '006 patent provides the general teaching that drug administration via the skin is divided into two categories: 1) transdermal administration and 2) intradermal administration (column 1, lines 39-41). Transdermal administration involves transport through the skin and into the blood stream to treat systemic diseases (column 1, lines 41-43). On the other hand, intradermal administration is intended to impart a cutaneous effect, while keeping the pharmacological effects of the drug localized to the intracutaneous regions of drug penetration and deposition (column 1, lines 43-47). Ideally, intradermal absorption occurs with little or no systemic absorption or accumulation.

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of the Falk '322 patent, concerning the treatment of skin diseases and conditions by administering a composition comprising a therapeutically effective amount of a non-toxic drug that inhibits prostaglandin synthesis with a therapeutically effective amount of hyaluronic acid, with the teachings of the Sakurai '224 patent, regarding the enzymatic decomposition and non-enzymatic oxidation-reduction of hyaluronic acid after being administered to a living body and how crosslinked hyaluronic acid is resistant to such decomposition, with the teachings of the Fischer '006 patent, regarding the two routes for administering a drug to the skin, either transdermal or intradermal. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested in the Sakurai '224 patent, that

crosslinked hyaluronic acid shows resistance to enzymatic decomposition or non-enzymatic oxidation-reduction decomposition (column 1, lines 54-59). Thus, one of ordinary skill in the art would know that the compound's half-life would be increased as it is no longer subjected to enzymatic and non-enzymatic oxidation-reduction decomposition. With regards to the route of administration, one of ordinary skill in the art would have been motivated to combine the teachings in order to receive the expected benefit, as suggested in the Fischer '006 patent, that intradermal administration imparts a cutaneous effect, while keeping the pharmacological effects of the drug localized to the intracutaneous regions of drug penetration and deposition, which ideally results in little or no systemic absorption or accumulation. Furthermore, as one of ordinary skill in the art is aware that the absorption, distribution, metabolism and excretion of a drug is critically influenced by its route of administration, it is considered within the capabilities of one of ordinary skill in the art to determine the best route of administration for a drug to achieve optimal treatment results.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicants' arguments, filed 23 March 2010, with respect to the rejection of claims 1-4, 9, 11-13 and 23 made under 35 USC § 103(a) as being unpatentable over U.S. Patent No. 5,914,322 to Falk *et al.*, in view of U.S. Patent No. 4,716,224 to Sakurai *et al.*, in view of U.S. Patent No. 6,455,066 B1 to Fischer *et al.*, have been fully

considered but they are not persuasive. The Declaration of Mr. Kiyoshi Kawamura, submitted by Applicants on 21 January 2010 under 37 CFR § 1.132, is not relevant to this rejection and therefore will not be addressed.

Applicants argue that the Fischer '066 patent does not teach intradermal administration of drugs or penetration agents for improving the absorption of a drug, but rather, teaches topical administration of a drug by applying the same combination with a suitable penetration agent. This argument is not persuasive because the teachings of the Fischer '066 patent was cited to teach that in addition to topical administration of a drug, transdermal and intradermal administration are also known methods for application of a drug via the skin. Similar to the topical form of administration disclosed by the Falk '322 patent, the Fischer '066 patent teaches that intradermal administration is intended to impart a cutaneous effect, while keeping the pharmacological effects of the drug localized to the intracutaneous region of drug penetration and deposition, thereby resulting in little or no systemic absorption. As such, it would have been *prima facie* obvious for one of ordinary skill in the art to administer the composition disclosed in the Falk '322 patent either topically, or intradermally, with the reasonable expectation that either method of administration would yield expected results.

The rejection is still deemed proper and therefore maintained.

Conclusion

No claim is allowed. This rejection is made NON-FINAL due to the new/modified grounds of rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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